EXPERIMENTAL CELL RESEARCH 317 (2011) 2759–2764

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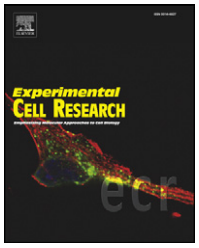

Review Article

The origin of pre-neoplastic metaplasia in the stomach: Chief cells emerge from the Mist

James R. Goldenring[a,b,*], *Ki Taek Nam*[a,b], *Jason C. Mills*[c]

[a]*Nashville Department of Veterans Affairs Medical Center, Nashville, TN, USA*
[b]*Departments of Surgery and Cell and Developmental Biology, Epithelial Biology Center, Vanderbilt University School of Medicine, Nashville, TN, USA*
[c]*Divison of Gastroenterology, Departments of Medicine, Pathology, and Developmental Biology, Washington University School of Medicine, St. Louis, MO, USA*

ARTICLE INFORMATION

Article Chronology:
Received 6 May 2011
Revised version received
23 August 2011
Accepted 24 August 2011
Available online 31 August 2011

Keywords:
Gastric adenocarcinoma
Metaplasia
SPEM
Intestinal metaplasia
Transdifferentiation
Chief cell
Zymogenic cell

ABSTRACT

The digestive-enzyme secreting, gastric epithelial chief (zymogenic) cell is remarkable and underappreciated. Here, we discuss how all available evidence suggests that mature chief cells in the adult, mammalian stomach are postmitotic, slowly turning over cells that arise via a relatively long-lived progenitor, the mucous neck cell, The differentiation of chief cells from neck cells does not involve cell division, and the neck cell has its own distinct pattern of gene expression and putative physiological function. Thus, the ontogeny of the normal chief cell lineage exemplifies transdifferentiation. Furthermore, under pathophysiogical loss of acid-secreting parietal cell, the chief cell lineage can itself trasndifferentiate into a mucous cell metaplasia designated Spasmolytic Polypeptide Expressing Metaplasia (SPEM). Especially in the presence of inflammation, this metaplastic lineage can regain proliferative capacity and, in humans may also further differentiate into intestinal metaplasia. The results indicate that gastric fundic lineages display remarkable plasticity in both physiological ontogeny and pathophysiological pre-neoplastic metaplasia.

Contents

* *Corresponding author at:* Vanderbilt University School of Medicine, Department of Surgery, Epithelial Biology Program, 10435G MRB IV, 2213 Garland Avenue, Nashville, TN 37232, USA. Fax: +1 615 343 1591.
E-mail address: jim.goldenring@vanderbilt.edu (J.R. Goldenring).

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doi:10.1016/j.yexcr.2011.08.017

Introduction

Normal chief cell location and function

The gastric epithelium is organized as a series of roughly funnel-shaped invaginations from the gastric lumen known as gastric units. In the glandular portion of the stomach (known in most species as the corpus or body) each gastric unit is broadest where it adjoins the gastric lumen proper. This broad pit region is lined by simple columnar, mucus-secreting epithelium. Below the pit zone, the gastric unit narrows into one or multiple glandular branches. In mammals, proliferative activity and the presumptive stem cell are located where the pit narrows into each gland in a small region known as the isthmus [1,2]. The glands secrete both digestive enzymes and acid, a function that can be performed by a single oxyntico-peptic cell in birds [3,4], whereas in mammals, these functions are divided into two autonomous lineages: acid-secreting parietal cells and digestive-enzyme (zymogenic) producing chief cells. Even in mammals, parietal and chief cells likely develop from a common progenitor [5,6]. Chief cells occupy most of the base of a gastric gland, the upper ones organized as simple cuboido-columnar cells, the lower ones outpouching into an acinar configuration at the very base [7]. Parietal cells can occur throughout the gastric unit, but the vast majority are located in the neck of the gland, between the isthmus and the base [8,9].

Normal chief cell maturation requires XBP1 and MIST1

The chief cell is a large cell with an extensive network of lamellar rough endoplasmic reticulum (rER), concentrated around the basally oriented nucleus, and numerous, large, apical exocrine secretory granules filled with digestive enzymes. Recent studies have identified the transcription factors regulating this specialized cellular architecture. Conditional deletion of X-Box Binding Protein 1, XBP1, in mice leads to small chief cells with only scattered, scant rER [10], consistent with the known role of XBP1 in inducing cellular rER formation. XBP1 directly induces the basic Helix-Loop-Helix (bHLH) transcription factor MIST1 (Fig. 1). MIST1 (BHLHA15) is required for the basal localization of the nucleus and the maintenance of substantial apical cytoplasm filled with abundant, large vesicles [11]. Thus, chief cell structure is seemingly completely dependent on an XBP1 to MIST1 sequence, wherein XBP1 directly induces the extensive rER network (for translation of all the digestive enzymes), and MIST1 in turn regulates the

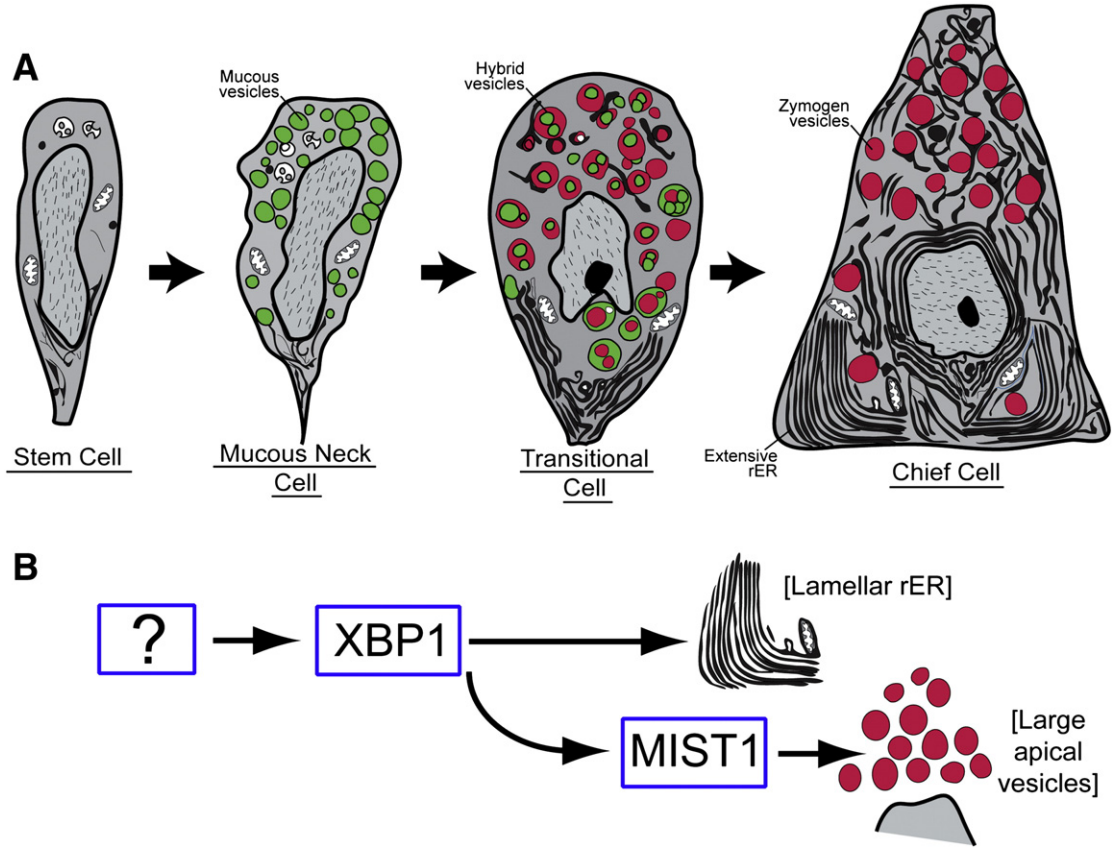

Fig. 1 – The cellular lineage ontogeny of normal gastric chief cells. A. Scheme for the origin of chief cell lineages from mucous neck cells. B. Transcription factor cascade responsible for maturation of normal chief cells.

development of vesicles containing the digestive enzymes and the secretory machinery to store and release them in a regulated fashion.

Chief cells normally arise by transdifferentiation

Normal chief cells do not derive directly from gastric epithelial progenitor cell lineages, but rather through an intermediate cell type, characterized by abundant mucinous vesicles in the neck of the gland (Fig. 1). These mucous neck cells do differentiate directly from the normal gland stem cell via recognizable precursor ("pre-neck") forms, thereafter migrating basally in amongst parietal cells in the neck until they rapidly transition into chief cells as they reach the base [12]. Mucous neck cells differ from chief cells in that they have their own distinct pattern of gene expression (e.g., *Gkn3*, *Tff2*, *Muc6*), a distinct morphology (they have thin projections to the basement membrane and broad apices facing the gastric unit lumen), and presumably thus a separate physiological function (to secrete mucins). However, there is little if any published evidence that demonstrates what the purpose of their mucus secretion, if it occurs, is. Nucleotide analog (^{3}H-thymidine, Bromodeoxyruidine) uptake experiments indicate that neck cells survive for 9–16 days [11,13]. Therefore, mucous neck cells appear to represent a separate lineage and, if they are progenitors for chief cells, this differentiation pattern of a long-lived cell with one phenotype from a relatively long-lived cell type with its own gene expression and morphology pattern is quite remarkable and may involve a number of heretofore unappreciated cellular differentiation mechanisms [12].

Because the process of mucous neck cell to chief cell differentiation does not require cell division, it represents an example of transdifferentiation. The evidence for this transdifferentiation from mucous neck to chief cell is extensive. First, as mentioned, nucleotide analog tracing shows that cells with chief and pre-chief cell morphology or marker expression, rarely, if ever, divide. Rather, it takes several days following nucleotide analog administration before the analogs are found in chief cells, indicating that chief cells arise from a precursor or intermediate [7,11]. In such studies, the nuclear-analog-positive cells that first appear are those with features hybrid between the chief and neck cells, and those hybrid cells are found at the transition between the neck and the base. Second, in almost every gland, there are cells at the transition between the neck and the base that co-express neck and chief cell markers [8,11] and, on electron microscopy and immune electron microscopy, have secretory granules containing both mucin and digestive enzymes [11,13,14]. Third, the first mature chief cells arise late in development, and a full complement is achieved only around the time of weaning in rats and mice. Immature glands are populated instead by cells with mixed neck-chief cell characteristics that gradually resolve into distinct neck and chief cell populations [15]. Similarly, injury [16] and transplantation [17] studies, not to mention studies of metaplasia that will be discussed later in this review, all indicate that cells with mucous neck cell and chief cell phenotypes are inter-convertible and hence simply two different manifestations or stages of the same lineage. Fourth, the transcription factor MIST1 is expressed only in chief cells and in about half of the cells with hybrid neck-chief cell characteristics in the transition between the neck and base zones. In *Mist1*$^{-/-}$ mice, there are significantly more cells of neck-chief hybrid phenotype, suggesting that loss of MIST1 causes a delay in the normal transition [11]. Chief cells arising after XBP1—which induces MIST1 and is thus further upstream in chief cell differentiation—is conditionally deleted, all show hybrid neck-chief cell characteristics.

In summary, nucleotide analog, morphological, developmental, pathophysiological, and molecular data support the remarkable conclusion that the chief cell lineage exhibits a dramatic phenotypic transition as part of its normal homeostasis. Furthermore, this differentiation pattern appears remarkably malleable, which we will examine further in subsequent sections.

Loss of parietal cells leads to transdifferentiation of mature chief cells into SPEM

While controversy exists as to the sequence and connection of mucosal lineage changes associated with increased risk for gastric cancer, there is a general agreement that the loss of acid secreting parietal cells, also known as oxyntic atrophy, is a prerequisite for induction of metaplasia [18]. A number of investigators over the past decade have therefore sought to identify aspects of the cascade of lineage changes associated with parietal cell loss. A seminal advance was the characterization of the *Helicobacter felis* infection model in C57BL/6 mice by Fox and Wang [19,20]. C57BL/6 mice infected with *H. felis* demonstrate progressive loss of parietal cells over 4–6 months of infection and the gastric mucosa is replaced with a mucous cell metaplasia in the gastric fundus with sparing of the gastric antrum. These metaplastic mucous cells express TFF2, also known as spasmolytic polypeptide, leading to the designation of this lineage as spasmolytic polypeptide-expressing metaplasia or SPEM [20,21]. SPEM was also identified in the mucosa surrounding intestinal type gastric cancers in humans [22]. This mucous cell lineage, which also expresses MUC6, is morphologically similar to the deep gland cells of the antrum or the Brunner's gland cells. Importantly, C57BL/6 mice infected with *H. felis* for over 9–12 months showed progression of the metaplasia to gastritis cystica profunda, with dysplastic glands penetrating into the submucosa and muscularis layers of the stomach wall [19,20]. These results indicated that, in the face of chronic parietal cell loss and inflammation, metaplastic glands could progress towards dysplasia.

In addition to this chronic model, methods for induction of acute oxyntic atrophy became available in 2000. Treatment of mice and rats with the neutrophil elastase inhibitor DMP-777 caused rapid loss of parietal cells from the gastric mucosa over 3–4 days of daily dosing [23,24]. This drug causes direct parietal cell death due to its action as a parietal cell-specific apical membrane protonophore, which allows entry of acid into parietal cells and specific cell toxicity. The effects of DMP-777 are ameliorated by pretreatment with omeprazole [25]. Following initial parietal cell loss, after 7–10 days of daily treatment, SPEM emerges from the bases of glands coincident with the appearance of scattered proliferative cells at the bases of fundic glands [23,24]. No significant changes are observed in the antrum. Importantly, while metaplastic lineages are maintained in mice and rats dosed for over a year with DMP-777, no evidence of gastritis cystica profunda or dysplasia develops, suggesting that inflammation is required for progression of metaplasia to neoplasia [23].

More recently we have examined the effects of a variant of DMP-777, designated L-635, which still possess strong parietal

cell protonophore activity, but does not show any inhibition of neutrophil elastase [26]. Like DMP-777, treatment of mice with L-635 leads to a rapid loss of parietal cells within 2–3 days of daily dosing. However, unlike DMP-777, the loss of parietal cells is accompanied by an exuberant inflammatory response. In L-635 treated mice, we observed development of prominent SPEM after only 3 days of treatment and the SPEM was highly proliferative. Indeed, the SPEM elicited by only 3 daily doses of L-635 induced a phenotype remarkably similar to that observed in mice infected with *H. felis* for 6–9 months [26]. Unfortunately, it remains unclear whether chronic dosing with L-635 would lead to dysplastic changes, as seen with *H. felis*, because of the very limited availability of the compound.

While all of these studies clearly linked the loss of parietal cells to the induction of SPEM, the question remained as to the origin of this metaplastic mucous cell lineage. Previous biases have suggested that metaplasias and dysplasias would arise from professional resident progenitor cells that alter their program of differentiation. However, a number of observations called into question the derivation of SPEM from normal progenitor cells, which are located above the neck of the gland, in the isthmus region. First, treatment with DMP-777 led to induction of SPEM initiated from the bottoms of gastric glands rather than from the isthmus [24]. Second, after 10–14 days of DMP-777 treatment, one can observe two groups of BrdU positive cells, one in the isthmus below foveolar hyperplastic surface mucous cells and one at the bases of fundic glands [23,24]. These results suggested that a second population of proliferative cells was induced following loss of parietal cells. While no Ki-67 staining was observed in normal chief cells, after induction of SPEM with acute parietal cell loss, Ki-67-staining were observed in the bases of fundic glands. Third, in the context of acute oxyntic atrophy, we observed cells at the bases of fundic glands with immunostaining for both TFF2 and intrinsic factor in separate secretory granules [24]. Electron microscopy analysis of these cells demonstrated the presence of zymogen granules and vesicles with mucous granule phenotype as well as other small clear vesicles. These findings contrast with those for pre-zymogenic cells, where hybrid granules containing both zymogens and mucins are observed [11]. Fourth, in the gastrin-deficient mouse model, where induction of SPEM is markedly accelerated in response to acute oxyntic atrophy, in mice treated for 1–2 days with DMP-777, we observed cells that were dually positive for both MIST1 and TFF2 [27]. All of these studies led to an initial impression that SPEM was evolving from MIST1-positive chief cells.

To evaluate this novel hypothesis for the origin of metaplasia from a mature post-mitotic lineage, we pursued a lineage mapping approach utilizing Mist1-CreERT2;Rosa26R(LacZ) mice [26]. Treatment of these mice with tamoxifen caused induction of Cre recombinase only in mature chief cells and resulted in the marking of these cells with the expression of bacterial β-galactosidase. After resting the mice for 10 days without treatment, the mice were then subjected to one of the three models of oxyntic atrophy and SPEM induction with acute treatment with DMP-777 for 14 days, acute treatment with L-635 for 3 days or infection with *H. felis* for 6 months. Remarkably, all three models demonstrated derivation of SPEM from mature chief cells marked with β-galactosidase expression [26]. However, the most dramatic lineage mapping was observed in the acute and chronic models of oxyntic atrophy associated with inflammation (L-635 treatment and *H. felis* infection, respectively), where essentially the entire SPEM lineage was derived from chief cells. These results indicate that the loss of parietal cells can induce transdifferentiation of chief cells into SPEM and that this metaplasia can undergo expansion under the influence of acute or chronic inflammatory infiltrates.

The relationship of SPEM to intestinal metaplasia

In humans, both SPEM and intestinal metaplasia are observed in the stomachs of gastric cancer patients. While SPEM possesses the characteristics of antral metaplasia, including expression of TFF2 and MUC6, intestinal metaplasia demonstrates clear lineage characteristics of the duodenum of intestines, with expression of TFF3 and MUC2 [28]. Nevertheless, while both metaplasias do exist in humans, it has been difficult to discern the relationship of these metaplasias because *Helicobacter* infection in mice does not result in intestinal metaplasia. Nevertheless, *H. pylori* infection of other species, such as Mongolian gerbils, does induce intestinal metaplasia and eventually dysplasia and cancer [29–33]. A recent study by Nomura and colleagues addressed the relationship of SPEM and intestinal metaplasia through a detailed examination of the histopathological changes associated with *H. pylori* infection in the Mongolian gerbil [33]. After 3 weeks of *H. pylori* infection, gerbils developed SPEM in the presence of parietal cell loss. While extension and expansion of SPEM was observed over the following weeks, after 24 weeks intestinal metaplasia arose from sites surrounded by mucosa with pre-existing SPEM. In single gland units these investigators observed goblet cell containing intestinal metaplasia (as marked by expression of MUC2) luminal to SPEM lineages expressing TFF2 [33]. In these glands, cells at the transition between SPEM and intestinal metaplasia expressed markers of both SPEM and intestinal metaplasia (e.g. MUC2 and TFF2).

While no intestinal metaplasia has been observed in *Helicobacter* sp.-infected mice, older amphiregulin mutant mice develop intestinal metaplasia and dysplasia in the setting of pre-existing SPEM [34]. As with the gerbils, SPEM developed spontaneously in amphiregulin-deficient mice after 9 months of age. In addition, MUC2-expressing intestinal metaplasia developed within glands also expressing SPEM markers after 1 year of age. As in the gerbils, hybrid cells expressing both MUC2 and TFF2 were observed in transition zones within dysplastic regions [34]. These results supported the concept that SPEM is the first metaplasia arising after induced oxyntic atrophy, and then, with subsequent on-going chronic inflammation, intestinal metaplasia arises as a second metaplastic transition (Fig. 2).

A similar relationship between SPEM and intestinal metaplasia likely exists in humans [35,36]. In the stomach, we have observed the presence of compound glands that demonstrate SPEM at their bases and intestinal metaplasia towards the surface. These studies support the concept that intestinal metaplasia evolves directly from pre-existing SPEM. However, another interpretation is also possible. It may be that loss of parietal cells is necessary but not sufficient for intestinal metaplasia, whereas loss of parietal cells is sufficient for SPEM. Thus, SPEM will always be present when there is new oxyntic atrophy and will also be present in the vicinity of any newly induced intestinal metaplasia. Recent evidence using MIST1, TFF2, and CDX2 as markers suggested SPEM and intestinal metaplasia in humans might also arise independently from transdifferentiating chief cells during parietal cell loss [37].

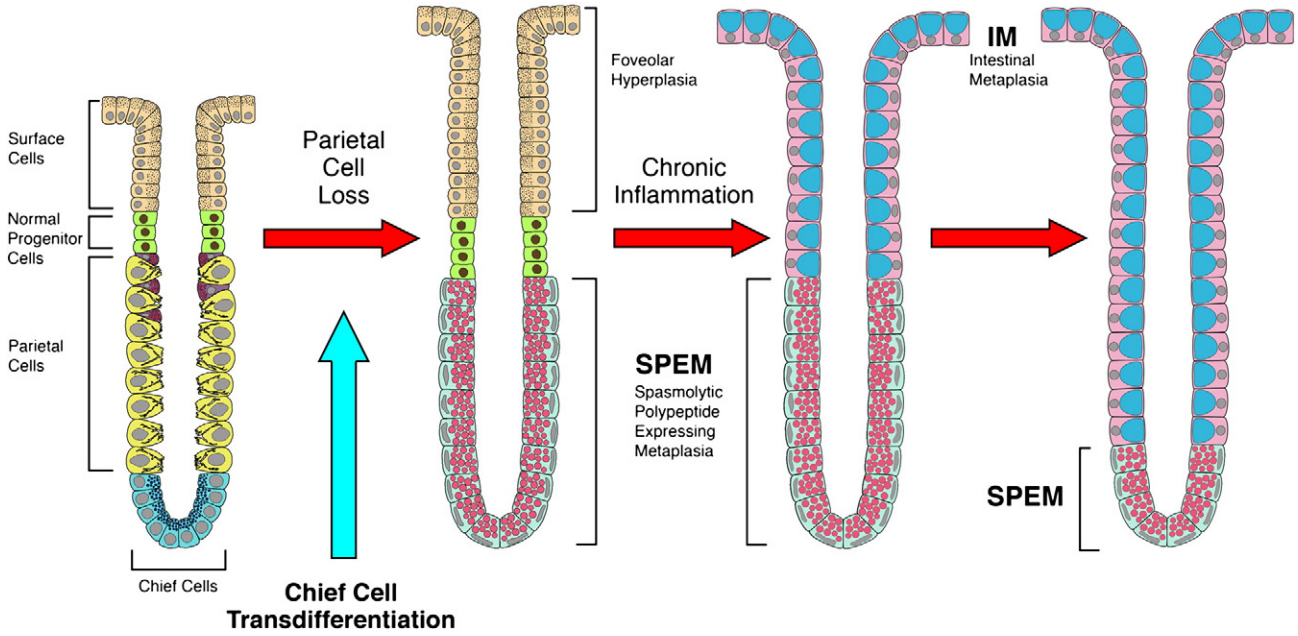

Fig. 2 – Current model for the origin and progression of gastric metaplasias. The preponderance of data indicates that chief cell transdifferentiation into SPEM is triggered by loss of parietal cells in the fundic mucosa. In the face of inflammation, SPEM can expand into a proliferative metaplasia. With continued chronic inflammation, intestinal metaplasia evolves in the setting of pre-existing SPEM and can come to dominate the entirety of the glands.

If intestinal metaplasia does arise directly from SPEM, it would be similar to the evolution of mucous cell metaplastic lineages reported by Wright and colleagues in the context of mucosal restitution in inflammatory bowel disease [38]. This induction of a second metaplastic transition may reflect the severity and chronicity of mucosal damage as well as indicate an increased risk for neoplastic transformation. Interestingly, recent studies by McDonald and colleagues have suggested that intestinal metaplasia glands are clonal [39]. However, a comparison of mutations in intestinal metaplasia glands and adjacent dysplasia identified mapping of mutations in less than 10% of samples. It therefore remains uncertain whether SPEM also gives rise to dysplastic lineages or whether the presence of mixed metaplasia is indicative of an unstable genetic milieu that gives rise to neoplastic transformation.

Summary

The gastric fundic mucosa demonstrates processes of transdifferentiation in both physiological lineage derivation as well as in the pathophysiology of mucous cell metaplasia. In the normal adult fundic mucosa, mucous neck cells transdifferentiate into chief cells as they migrate towards the bases of fundic glands. This mucous cell to zymogen cell transition occurs without any intervening cell division to produce a chief cell population that by all standard criteria is postmitotic. Nevertheless, in the presence of significant parietal cell loss, chief cells can go through a process for zymogen cell to mucous cell transdifferentiation that leads to the formation of mucous cell metaplasia. This pathophysiological transdifferentiation, especially in the presence of inflammatory influences can lead to recrudescence of proliferative capacity. While previous studies have indicated that transdifferentiation of chief cells into SPEM is associated with upregulation of a number of proteins associated with DNA unwinding (e.g. MCM proteins) [27]. However, overall, the cellular and molecular pathways used to reshape lineage secretory profiles, both physiologically and pathophysiologically, largely remain a mystery investigated by only a handful of studies to date. If we are to understand the process of gastric carcinogenesis, we must understand both how SPEM is induced by parietal cell loss and the relationship of SPEM to intestinal metaplasia and ultimately dysplasia. Future studies should give new insights into the cellular mechanisms responsible for the remarkable plasticity of gastric fundic lineages.

Acknowledgments

Dr. Goldenring and Dr. Mills have both been supported by the AGA Funderburg Award in Gastric Biology Related to Cancer. Dr. Goldenring is also supported by grants from a Department of Veterans Affairs Merit Review Award, RO1 DK071590 from the National Institutes of Health, and by core resources of the Vanderbilt Digestive Disease Center, P30 DK058404. Dr. Mills is also supported by DDC-115769 from the American Cancer Society and R01 DK-079798 and P30 DK052574 (the Washington University DDRCC), both from the National Institute of Diabetes and Digestive and Kidney Disease.

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